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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MAIER, LEIGH C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,669	KARLSSON ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on 17 March 2004.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 3,4,8-12,14,30-35,37-52,54 and 56-64 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 3,4,8-12,14,30-35,37-52,54 and 56-64 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 3, 8, 39, 52, and 56 have been amended. Claims 57-64 have been added. Claims 3, 4, 6, 8-12, 14, 30-35, 37-52, 54, and 56-64 are pending. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Any objection or rejection not expressly repeated has been withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 17 March 2004 has been entered. The remarks accompanying the RCE have been fully considered and are addressed below.

Claim Objections

Claims 57-60 are newly submitted claims and are properly designated as "new." However, the text of the two lines of the claims is underlined. In order for new claims to be compliant with "mark-up" rules, new claims are to be designated as such. They may be fully underlined or not underlined at all, but they cannot be partially underlined. This appears to be simply a typographical error.

Claim Rejections - 35 USC § 112 – 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 4, 6, 8-12, 14, 30-35, 37-52, 54, and 56-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims have been amended to include the limitations concerning "unknown foreign steroids" wherein these "unknown foreign steroids" are "formed from the degradation of the glucocorticosteroid." These "unknown foreign steroids" are either essentially excluded or allowed in small amounts. Table 1 in the specification indicates the amount of "known foreign steroids" and "unknown foreign steroids." However, this does not adequately describe what an "unknown foreign steroid" is. In order for the claims to comply with the requirement of adequate written description, all components, those which are included and specifically excluded, must also be adequately described.

Claim Rejections - 35 USC § 112 – 2nd paragraph

Claims 3, 4, 6, 8-12, 14, 30-35, 37-52, 54, and 56-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims have been amended to include the limitations concerning "unknown foreign steroids" and "known foreign steroids" wherein these foreign steroids are "formed from the degradation of the glucocorticosteroid." Table 1 in the specification indicates the amount of "known foreign steroids" and "unknown foreign steroids." However, these are not terms that have any particular art-accepted meaning. Further, with the analytical methods available, one of ordinary skill would theoretically be able to characterize any degradation product. Therefore, these terms appear to be arbitrary distinctions based on what Applicant has and has not characterized, and one or ordinary skill would not be apprised of the metes and bounds of the claims. The claims are thus rendered vague and indefinite.

Claim 56 has been amended to remove some of the previously recited properties and now recites "the particles have essentially the same chemical purity and physical form as the particles before sterilization." The claim remains indefinite. As noted previously, a product may be claimed in a product-by-process form. However, the product *per se* still must be identifiable in the absence of knowledge of its method of production or the characteristics of its precursor. It appears to be Applicant's position that sterilization by irradiation introduces degradation products, so the product would be identifiable by the *absence* of said degradation products. This argument is unpersuasive. Leaving aside the lack of description of said products, take an example where a product is sterilized by irradiation. Later, with no change in chemical purity or physical form of the sterilized product, this product is rendered nonsterile, so that sterilization is again required. This time sterilization is conducted by the method disclosed in the present specification. By Applicant's argument, the product, after the second sterilization, would be essentially identical to the product as it was before the heat treatment, yet it would contain

degradation products therefore not distinguishable from the irradiated product. Furthermore, it has not been established what the purported irradiation degradation products are and if they are different than those produced by other means of degradation.

Claim Rejections - 35 U.S.C. § 103

Claims 3, 4, 6, 34, 35, 39, 41,42, 45-47, 49-52, 54, 56, 57, 59-61, 63, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) and BUSSEY et al (J. Parenter. Sci. Tech., 1983).

The invention is as described in previous Office actions. The independent claims have been amended to add limitations regarding maximum amounts of "known" and "unknown foreign steroids."

Independent claim 39 has been amended to require a pharmaceutically acceptable inhalation powder comprising a glucocorticosteroid in the form of sterile, finely divided particles. The claim recites that the particles be heat sterilized. Dependent claims recite limitations regarding particle size and conditions for heat sterilization.

Independent claims 49-52 are drawn to heat-sterilized glucocorticosteroid products, similar to those described above. New claims 57-60 recite products "in which the powder contains not more than 0.38% known and unknown foreign steroids formed from the degradation of the glucocorticosteroid."

JAKUPOVIC teaches a crystalline form of the anti-inflammatory agent, budesonide, in which 90% of the particles have a diameter of less than 5.7 μm, for nasal inhalation in treating diseases of the respiratory tract. See example 1, page 8 and page 4, lines 4-6. The reference

further teaches a particle range of about 0.1 μm to about 10 μm. See paragraph bridging pages 3 and 4. The reference also teaches the use of other glucocorticosteroids, such as rofleponide and mometasone. The reference further teaches the preparation of pharmaceutical compositions by adding any of a variety of pharmaceutically acceptable carriers. See page 5, beginning line 11, continuing through page 6, line 17.

JAKUPOVIC does not teach a sterile product. The reference further does not teach the percentage by weight of the glucocorticosteroid.

BUSSEY teaches the sterilization of (gluco)corticosteroid powders by ^{60}Co irradiation. See entire reference, particularly the abstract. The claim also teaches that ethylene oxide is used to sterilize bulk steroids. See introduction. The reference is silent with regard to the production of "unknown foreign steroids."

It would have been obvious to one having ordinary skill in the art at the time the invention was made to sterilize the respirable, dry powders disclosed by JAKUPOVIC by either irradiation or treatment with ethylene oxide. The artisan would have been motivated to sterilize the respirable particles to prevent microbial growth in the packaged material with a reasonable expectation of success. The artisan would be particularly motivated to sterilize the glucocorticosteroid in the form that it is intended to be used.

It would also be obvious to the ordinarily skilled worker to purify the glucocorticosteroid (prepare in a form having a high percentage of the glucocorticosteroid by weight) in order to limit contaminants in products for human administration. With regard to new claims 57, 59, and 60, (and purity levels in general) it appears to be Applicant's position that a radiolytic sterilization process would result in a glucocorticosteroid comprising degradation products in a

greater percentage than that recited in the claims. However, it is noted that the claimed products are powders *comprising* a glucocorticosteroid, not limited to a glucocorticosteroid, *per se*. As discussed previously, it would be further obvious to prepare pharmaceutical compositions for their art-disclosed utility, as described by JAKUPOVIC. Even if the disclosed radiolytic sterilization process did result in a greater level of degradation products, these degradation products would be diluted by the addition of carriers taught by JAKUPOVIC to provide a lower *overall* percentage.

Applicant contends that BUSSEY does not "teach anything about the desirability of sterile pharmaceutical products" or "indicate any advantage of sterile steroids." The examiner respectfully disagrees. The "Results and Discussion" section discusses the reduced bioburden of various microorganisms upon radiolytic sterilization. The very fact that the presence of microorganisms is called a bio*burden,* and not biohelper or even bioneutral, is telling. Further, the spores are also called "contaminants." Finally, the reference teaches that "the sterilizing dose . . . gives added safety factor." See page 53, 2nd and 3rd full paragraphs. The examiner maintains that one of ordinary skill would in fact surmise that sterilization of steroid products is advantageous.

Applicant further contends that the FDA does not require that inhalation powders be sterile and submits an FDA document to support this. The examiner does not find a document published after Applicant's earliest priority date and labeled "Draft – Not for Implementation" and "for comment purposes only" to be germane to the present prosecution.

Claims 3, 4, 6, 8-12, 14, 30, 31, 34, 35, 39, 41-52, 54, and 56-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) and BUSSEY et al (J. Parenter. Sci. Tech., 1983), in view of SEQUIEIRA et al (US 5,837,699).

The invention is as set forth previously and amended as discussed above.

JAKUPOVIC teaches as set forth above. The reference teaches treatment of diseases of the respiratory tract in general, but not the particular disorders recited in the claims. The reference teaches the preparation of pharmaceutical compositions, but not specifically suspensions.

BUSSEY teaches as set forth above.

SEQUIEIRA teaches nasal inhalation of a number of (gluco)corticosteroids including budesonide and mometasone for the treatment of specific respiratory disorders, such as COPD, asthma, and rhinitis. See col 1-2. The reference further teaches administration of the glucocorticosteroid as a dry powder or as an aqueous suspension of about 0.01 to about 10 mg of glucocorticosteroid to gram of suspension. See col 5. Given that 1g water = 1ml water, this range is approximately the same as the concentrations (mg/ml) recited in the claims.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use the dry, sterile glucocorticosteroids or as aqueous suspensions of said glucocorticosteroids for the treatment of the recited respiratory disorders for their art-disclosed utility. It would be within the scope of the artisan to optimize the dosage and prepare suspensions of appropriate concentration for said dosage through routine experimentation.

Applicant reiterates arguments discussed above and further contends that SEQUIEIRA does not teach all the limitations of the present invention. However, the rejection is clearly stated

as one of obviousness. Applicant also argues that there is no motivation to combine the references. The examiner maintains that the references are properly combined for reasons set forth above.

Claims 3, 4, 6, 32-35, 39-42, 45-47, 49-52, 54, 56-61, 63, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) and BUSSEY et al (J. Parenter. Sci. Tech., 1983), in view of RADHAKRISHNAN et al (US 5,192,528).

The invention is as set forth previously and amended as discussed above.

JAKUPOVIC teaches as set forth above. The aim of the reference is preparation of glucocorticosteroids available to the lower respiratory tract. See page 1, lines 9-15. As noted above, JAKUPOVIC teaches the range of particles of about 0.1 μm to about 10 μm, but the reference does not specifically exemplify particles of less than 5 μm. However, the reference teaches how the size of the particles may be controlled by process parameters that one of ordinary skill would be able to optimize with routine experimentation.

BUSSEY teaches as set forth above.

RADHAKRISHNAN teaches that aerosol particles of corticosteroid formulations must be must be less than about 1 μm in order to reach the lower region of the respiratory tract (alveoli). See figure 1; col 5, lines 37-48; and col 7, lines 57-63.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare glucocorticosteroid in the form of sterile, respirable particles with MMD of less than 1 μm. The artisan would have been motivated to prepare this size in order for the respirable glucocorticosteroid to reach the alveoli during treatment with a reasonable

expectation of success. The artisan would be motivated to sterilize the product for reasons described above. Purity limitations are addressed above.

Applicant reiterates arguments discussed above. Applicant further argues that RADHAKRISHNAN teaches aqueous liposomal suspensions, inhalation powders. However, the reference was used to teach particle size, not the form of the composition. Applicant also argues that there is no motivation to combine the references. The examiner maintains that the references are properly combined for reasons set forth above.

Claims 3, 4, 6, 8-12, 14, 30-35, 37-52, 54, and 56-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over JAKUPOVIC et al (WO 96/32095) and BUSSEY et al (J. Parenter. Sci. Tech., 1983), in view of SEQUIEIRA et al (US 5,837,699) and RADHAKRISHNAN et al (US 5,192,528).

The invention is as set forth previously and amended as discussed above.

JAKUPOVIC and BUSSEY teach as set forth above. The references do not teach a suspension comprising sterile particles wherein the particles have MMD of less than 4 μm.

SEQUIEIRA and RADHAKRISHNAN teach as set forth above.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare sterile powder and prepare a suspension as set forth above. One of ordinary skill would be motivated to prepare a suspension comprising particles having MMD of less than 4 μm because SEQUIEIRA had taught the utility of these glucocorticosteroids in suspension for the treatment of a number of respiratory disorders, and RADHAKRISHNAN had taught that particles of this size are necessary for delivering the compounds to the lower

respiratory tract. These suspensions are taught in dosage levels suggesting concentrations embraced by that recited in the claims.

Applicant presents no new arguments other than lack of motivation to combine. The examiner maintains that the references are properly combined for reasons set forth above.

Conclusion

It is the examiner's position that it may be that Applicant is able to provide a sterile glucocorticosteroid, *per se*, having a particular minimum purity with the process described in the present specification, as has been discussed previously. However there is not enough data to make that determination at this point. This could be determined in a side-by-side test wherein the claimed glucocorticosteroids are sterilized to the same level of microorganism bioburden by the instant process and irradiation with a comparison of the resulting purity of each product.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Wednesday, or Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (571) 272-0661, may be contacted. The fax number for Group 1600, Art Unit 1623 is (703) 872-9306.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more.

Leigh C. Maier
Patent Examiner
May 25, 2004